Journal of the American College of Cardiology
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Published by Elsevier Science Inc.

Vol. 37, No. 2, 2001
ISSN 0735-1097/01/$20.00
PII S0735-1097(00)01119-0

Correlation of Coronary Calcification and Angiographically Documented Stenoses in Patients With Suspected Coronary Artery Disease: Results of 1,764 Patients

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OBJECTIVES This study correlated the electron beam computed tomographic (EBCT) calcium scores with the results of coronary angiography in symptomatic patients in order to assess its value to predict or exclude significant coronary artery disease (CAD).

BACKGROUND Electron beam computed tomography is a sensitive method to detect coronary calcium. However, it is unclear whether it may play a role as a filter before invasive procedures in symptomatic patients.

METHODS A total of 1,764 patients (1,225 men and 539 women) with suspected CAD from a single center were included in our study. All patients underwent calcium screening with EBCT (C150XP Imatron) and conventional coronary angiography.

RESULTS Fifty-six percent of men and 47% of women revealed significant coronary stenoses (≥50%). Total exclusion of coronary calcium (14% of the study group) was associated with an extremely low probability of stenosis (<1%). With calcium scores ≥20th, ≥100th or ≥75th percentile of age groups, the sensitivity to detect stenoses decreased to 97%, 93% and 81%, respectively, in men and to 98%, 82% and 76%, respectively, in women. At the same time, the specificity increased up to 77% in men and women. There was a significant difference in coronary calcium between men and women in all age groups; however, receiver-operating characteristic curves indicated that the test can be performed with equal accuracy in all of these subgroups.

CONCLUSIONS Calcium screening with EBCT is a highly sensitive and moderately specific test to predict stenotic disease. Exclusion of coronary calcium defines a substantial subgroup of patients, albeit symptomatic, with a very low probability of significant stenoses. (J Am Coll Cardiol 2001;37:451–7) © 2001 by the American College of Cardiology

Electron beam computed tomography (EBCT) can accurately detect coronary calcium, which indicates the presence of coronary atherosclerosis (1–5). Coronary calcium, as seen in the early stage of coronary artery disease (CAD), is closely correlated with fatty "soft" plaques, which may rupture and cause myocardial infarction (6,7). However, the correlation between arterial mineralization and the probability of plaque rupture is unknown. In symptomatic patients, EBCT calcium screening has been used to estimate the severity of stenosis. No close correlation, however, could be found between the amount of calcium and arterial lumen narrowing (8–13). In this study, we included 1,764 symptomatic patients with suspected CAD and compared the findings of coronary calcium screening, as assessed with EBCT and conventional coronary arteriography.

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Manuscript received March 17, 2000; revised manuscript received August 28, 2000, accepted October 4, 2000.

METHODS

Calcium screening. Electron beam computed tomography (C150XP Imatron) was used to determine coronary calcium. The scanner operated in the high resolution volume mode (630 mA, 130 kV, scanning time 100 ms, 40 slices à 3 mm, 512 × 512 matrix, 26-cm field of view, sharp kernel). Prospective electrocardiographic triggering in mid-diastole (80% of the RR interval) was applied during a single inspiratory breath-hold. The calcium score was calculated with Imatron's implemented software, according to the method of Agatston et al. (14). A calcified plaque was defined as a lesion of at least two adjacent pixels (>0.51 mm^2) with a signal density >130 Houndsfield units.

Coronary angiography. The Judkin's technique was used with at least four views of the left system and two views of the right system. Analysis of the coronary angiograms was done by an independent, experienced observer who was unaware of the calcium score. The decision to perform angiography was not influenced by the calcium score. Angiography was performed within four days after the

Abbreviations and Acronyms
CAD = coronary artery disease
EBCT = electron beam computed tomography
ROC = receiver-operating characteristic

EBCT scan in 78%, within 10 days in 98% and within 30 days in the remaining 2% of the patients. Significant stenosis was defined as ≥50% lumen narrowing of any epicardial coronary artery.

Patient group. A total of 1,764 consecutive patients who were referred for coronary angiography because of suspected CAD were included in this single-center study. All patients fulfilled the following inclusion criteria: typical or atypical chest pain and/or signs of myocardial ischemia on noninvasive tests (bicycle stress test, in most cases) and a clinical indication for cardiac catheterization. Patients were excluded if they had CAD documented by before cardiac catheterization or were specifically referred for coronary interventions. Thus, at the time of angiography, the patient's diagnosis was unclear. Consecutive patients fulfilling these criteria from July 1997 to November 1999 were included in this study. They form a subset from a total of 5,300 patients who underwent cardiac catheterization with coronary angiography at our institution during this period.

Statistical analysis. Because of the non-normality, statistical analysis was performed on the base 10 log of the transformed calcium score. The Wilcoxon signed rank test for unpaired data was used to compare the calcium score in different age groups and between men and women with and without significant CAD. Receiver-operating characteristic (ROC) curve analysis was performed as follows: the true positive rate (sensitivity) was plotted as a function of a false positive rate (1 − specificity) for predicting ≥50% angiographic stenoses for all possible threshold calcium scores. The ROC curve areas are given for all age groups. A curve area of 1.0 represents a perfect test, with 100% sensitivity and 100% specificity. Curve areas ≥0.7 indicate a reasonably good clinical test. In addition, coronary calcium scores in each age group were ranked in ascending order to calculate percentiles. Patients with calcium scores in the highest quartile (≥75%) were analyzed separately.

RESULTS

The study comprised 1,225 men and 539 women between 20 and 80 years old (56 ± 14 years in men and 60 ± 16 years in women, p = NS). "Chest pain" compatible with angina was reported by 65% of the patients. A stress test was available in 920 patients, which was abnormal (including borderline results) in 52%. Forty-one percent of the individuals were smokers. Coronary angiography revealed significant CAD (≥50% stenosis) in 56% of men and 47% of women (high grade stenosis ≥75% in 37% of men and 30% of women). There were 302 men (25%) and 220 women (41%) with normal coronary arteriograms. Diagnostic arteriography resulted in interventions in 463 patients (75% of patients with stenosis ≥75%) (percutaneous transluminal coronary angioplasty with or without stent implantation, coronary artery bypass graft surgery in 12 patients).

The calcium scores for men and women (Tables 1 and 2) indicate that: 1) the mean score in men was significantly higher than that in women ($p < 0.0001$) at each age class; 2) for both genders, there was a significant increase in calcification with age; 3) the variability of scores within each age class was high (as indicated by the high standard deviation); this was caused by a minority of patients with excessive calcification; and 4) the difference between patients with and without significant CAD was highly significant for the total group of patients and within each age group.

Table 1. Calcium Scores in Symptomatic Men and Women

	Men		Women	
	n	Score	n	Score
Without significant CAD				
Age (years)				
<40	78	4 ± 8	86	5 ± 11
40–50	93	36 ± 88	25	4 ± 15
50–60	164	115 ± 345	45	45 ± 126
60–70	149	191 ± 328	80	53 ± 89
>70	56	275 ± 308	48	151 ± 211
Σ	540	123 ± 289*	284	49 ± 121*
With significant CAD (≥50% stenosis)				
Age (years)				
<40	91	122 ± 184	39	108 ± 162
40–50	96	358 ± 590	56	116 ± 265
50–60	156	620 ± 910	46	222 ± 374
60–70	202	862 ± 1,066	67	396 ± 522
>70	140	1,196 ± 1,407	47	942 ± 1,146
Σ	685	706 ± 1,047*	255	360 ± 665*

*$p < 0.001$, also true for all age groups. Score values are presented as the mean ± SD.
CAD = coronary artery disease.

Table 2. Calcium Score Nomogram for 1,764 Symptomatic Subjects

	Age (yrs)				
	<40	**40–50**	**50–60**	**60–70**	**>70**
Men (n = 1,225)	n = 169	n = 189	n = 320	n = 351	n = 196
25th percentile	0	34	61	156	176
50th percentile	23	78	193	342	407
75th percentile	45	229	593	670	1,068
90th percentile	156	576	954	1,562	2,694
Women (n = 539)	n = 125	n = 81	n = 91	n = 147	n = 95
25th percentile	0	0	18	46	68
50th percentile	0	27	42	127	362
75th percentile	552	67	168	208	697
90th percentile	138	148	467	523	1,498

Exclusion of coronary calcium. No calcium was found in 128 (23.7%) of 540 men and in 116 (40.8%) of 284 women without significant CAD, as compared with 5 (0.7%) of 685 men and 0 of 255 women with coronary stenoses ≥50% (Table 3). Thus, exclusion of coronary calcification was associated with an extremely low probability of significant stenosis in men and women. In contrast, there was a considerable number of patients without stenoses who, although symptomatic, did not reveal any calcification: 55% of symptomatic men and women <40 years of age had no calcification. In this group, the risk of stenosis was 0%. The prevalence of "no calcium" decreased with age, but even in the age group 60 to 70 years, 12% of men and 32% of women were free of calcium and had no apparent risk of significant coronary lesions (Table 3). However, even the complete absence of coronary calcium did not totally exclude high grade coronary stenosis, although this was a very rare finding (n = 5, only 2 of whom required intervention).

Accuracy of the test at different score levels. The positive finding of coronary calcium (score >0), as expected, had the best sensitivity (99% in men and 100% in women) and the best negative predictive power (97% in men and 100% in women) to detect stenosis ≥50% and stenosis ≥75% in men and women (Table 4, upper left panel). The specificity (23% in men and 40% in women) was poor, and the positive predictive value of this variable was moderate.

A score ≥20 was sensitive, but only moderately specific, to detect stenosis (Table 4, upper right panel). In contrast, a score <20 was a powerful variable to exclude stenotic disease: only 16 (5.9%) of 267 men (22% of study group) and 1 (0.5%) of 183 women (34% of study group) with a score ≤20 had significant CAD.

Several more patients had a score ≥100 (Table 4, lower left panel), indicating severe plaque burden, and sensitivity was reduced, especially in women.

Score values in the ≥75th percentile of the age group were even less sensitive, but resulted in the best specificity in women.

The ROC curve areas for all age groups and both genders with significant CAD (≥50% stenosis) are given in Table 5. The values are all >0.75, indicating that the test can be performed with similar accuracy in all age groups, irrespective of gender.

Clinical useful score cutpoints for management decisions. In Figure 1 (for men) and Figure 2 (for women), the scores are divided into three levels for each age group: the lower range defines 95% of patients without significant stenoses. Thus, up to the lower score threshold, significant CAD in a symptomatic person is very unlikely. The upper range includes 90% of patients with significant stenoses. Calcium levels beyond the upper score threshold are associated with obstructive disease in the majority of patients. In the white zone, diagnosis is uncertain. The white zone consisted of 98 men (8%) and 40 women (7.4%). A narrow white area indicates an excellent test variable, with only a few patients in the indefinite zone (approaching a "yes" or

Table 3. Exclusion of Coronary Calcium (Score = 0)

	Men		Women	
	Significant CAD (Stenosis ≥50%)			
	No	**Yes**	**No**	**Yes**
Age (years)				
<40	43/78 (55%)	0/91 (0%)	47/86 (55%)	0/39
40–50	30/93 (32%)	1/96 (1%)	21/25 (84%)	0/56
50–60	35/164 (21%)	2/156 (1%)	18/45 (40%)	0/46
60–70	18/149 (12%)	1/202 (0%)	26/80 (32%)	0/67
>70	2/56 (4%)	1/140 (1%)	4/48 (8%)	0/47
Total	128/540 (24%)	5/685 (0.7%)	116/284 (41%)	0/255

Data are presented as the number of patients with score = 0/total number of patients in that age group, with percentages in parentheses.

CAD = coronary artery disease.

Table 4. Sensitivity and Specificity of Coronary Calcifications at Different Score Levels

	Score >0 ("Any Calcium Detected")				Score ≥20			
	Stenosis				Stenosis			
	≥50%		≥75%		≥50%		≥75%	
	M	F	M	F	M	F	M	F
Sensitivity	99%	100%	99%	99%	97%	98%	98%	98%
Specificity	23%	40%	39%	49%	62%	69%	51%	64%
PPV	62%	66%	57%	53%	62%	70%	48%	59%
NPV	97%	100%	99%	99%	95%	91%	96%	94%
	Score ≥100				Score ≥75% Percentile of Age Group			
	Stenosis				Stenosis			
	≥50%		≥75%		≥50%		≥75%	
	M	F	M	F	M	F	M	F
Sensitivity	93%	82%	95%	89%	81%	76%	78%	75%
Specificity	75%	76%	79%	79%	72%	77%	83%	85%
PPV	76%	78%	71%	73%	65%	71%	67%	72%
NPV	79%	72%	85%	81%	70%	69%	77%	75%

NPV = negative predictive value; PPV = positive predictive value.

"no" decision). According to this, EBCT calcium screening was especially helpful in men <50 years old and in women <60 years old.

DISCUSSION

This study describes the value of EBCT calcium screening in symptomatic patients who were referred to our center with suspected CAD to be proven or excluded by coronary angiography. The strength of this study is that all the patients were evaluated in a single center with the same technology; EBCT scans and angiography were performed within a few days of each other and were read by independent observers in a blinded manner. It is the largest study published. The main results are as follows: exclusion of coronary calcium was associated with a very low risk of significant CAD (<1%). Eleven percent of men and 22% of women, although symptomatic with a high pretest probability of CAD and an indication for coronary angiography, did not show any coronary calcium; thus, this variable appears to be helpful as a filter before invasive procedures. Higher calcium score values (≥20th, ≥100th and ≥75th percentile of a given age group) are associated with decreased sensitivity to detect significant CAD, but increased specificity of the method. The quantification of calcium allowed exclusion of atherosclerotic disease in a subset of patients, and strongly predicted obstructive disease in others. There was a significant difference in coronary calcium between men and women of all age groups; however, the reliability of calcium testing in predicting significant stenosis was equally effective in men and women. Finally, the diagnostic benefit of calcium screening is maintained for all age groups.

Mechanism of calcification. Coronary calcium predominantly consists of calcium phosphate (hydroxyapatite), which is not only absorbed or deposited passively, but also forms in situ by an organized, regulated process (15–17). Coronary calcium is strongly associated with the total plaque burden, as has been evaluated in histopathologic studies (1,2). It is not a direct marker of the vulnerable plaque at risk of rupture; however, the greater the calcium score, the greater the potential for increased numbers of potentially lipid-rich plaques, which are widely thought to be the culprit lesions of acute coronary syndromes. Lesser obstructive plaques are associated with a higher incidence of coronary occlusion, as compared with severely obstructed plaques. This occurs not because of the higher risk of such

Table 5. Receiver-Operating Characteristic Curve Areas for Patients in Different Age Group, Gender and Presence of Coronary Artery Disease

Age (years)	Without Significant CAD		With Significant CAD (>50%)	
	Women	Men	Women	Men
<40	0.83	0.86	0.83	0.91
40–50	0.76	0.79	0.87	0.84
50–60	0.87	0.79	0.86	0.81
60–70	0.78	0.89	0.79	0.84
>70	0.79	0.81	0.83	0.82

CAD = coronary artery disease.

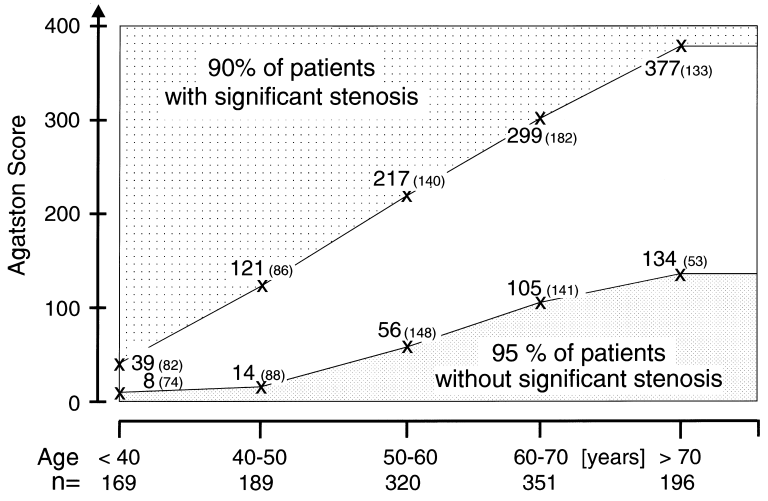

Figure 1. Diagnostic yield of calcium screening in symptomatic men. The lower scores define the calcium score thresholds for the 95% of patients *without* significant stenoses. The higher scores give the calcium score thresholds for the 90% of patients *with* significant stenoses. Within the central area, the diagnosis is uncertain. The numbers in parentheses give the number of patients within the area. For example, a man at the age of 50 years is probably free of coronary stenosis if his score is <56. At score values >217, he bears a high risk of stenosis.

plaques in and of themselves, but because of their much greater number (6). Angiography is not the gold standard to validate the significance of coronary calcification. Major discrepancies have been found between the angiographic severity of lesions and postmortem examinations (18–23), with angiography underestimating the extent of atherosclerosis (4,24). Morphology and functional consequence of stenoses may differ substantially (25,26).

Study group selected. The results should be seen in the light of the selection criteria chosen. We included patients who were referred for invasive coronary angiography because of symptoms suspicious of CAD. Our patients had typical or atypical chest pain and/or signs of ischemia during bicycle stress tests, which were borderline or inconclusive in many patients (e.g., those with ST segment abnormalities that failed to reach significance or those whose interpretation was difficult because of bundle branch block or female gender). Thus, the pretest probability of CAD in this patient group was high (~50% of the patients had significant stenoses). In contrast, the use of symptoms and conventional noninvasive methods turned out to be quite poor in predicting obstructive disease at angiography (*only* 50% had stenoses). Seventy-five percent of the patients with ≥75% stenoses went on to therapeutic interventions, but this group amounted to only 26% of the total group studied. This is in good agreement with the experience of other centers using interventional procedures in about one of three diagnostic tests, ranging from 1:1 to 1:4 at different sites. For all of the patients in our center, 65% of the diagnostic procedures led to interventions.

Diagnostic yield. Our results show that EBCT calcium screening can identify a subset of patients with a very low risk of significant CAD in whom invasive diagnostic procedures may be omitted. Absence of coronary calcium (11% of men and 22% of women) was associated with a very low probability of obstructive disease (0.7% in men and 0% in

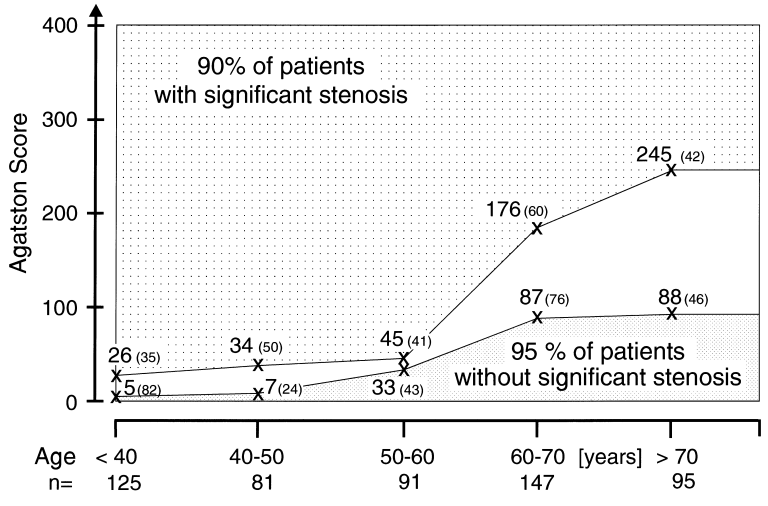

Figure 2. Diagnostic yield of calcium screening in symptomatic women. For explanation, see Figure 1.

women). Patients with high grade stenoses, but no calcification, are extremely rare.

There is no agreement on what score cutpoint should be used in the clinical setting. Some studies solely used exclusion of any calcium (8–12,27). Other studies used a fixed score of 100 (28) or an optimized cutoff value, irrespective of age and gender (8). Our study group is large enough to calculate cutpoints for each decade of age and separately for men and women.

Calcium screening with EBCT was especially helpful in patients up to the age of 50 years. In this age group, the prevalence of "no calcium" is higher (21% in men and 33% in women), and the "white zone" (Fig. 1 and 2) is small. These findings are consistent with some previous reports (9,12), but not with others (11,29). The differences are probably due to the selection criteria and the small numbers in these studies.

Analysis of the ROC area (Table 5) indicates that the ability to identify patients with coronary obstructive disease is equally good in all age groups, irrespective of gender, and is better than conventional bicycle stress testing (ROC area ~0.75) (30). The diagnostic accuracy of EBCT calcium screening has been found to be superior to conventional risk factor analysis (31) and equal to or better than conventional stress tests. The exercise stress test is characterized by a wide variability of sensitivity, specificity and diagnostic accuracy (mean sensitivity 81% [range 40% to 100%], specificity 66% [range 17% to 100%]) (32). The test results are influenced by gender, drugs, bundle branch block and an inability to exercise sufficiently. Moreover, the test is not free of complications (32–34). In contrast, EBCT calcium screening can be performed quickly, cost-effectively and with no risk to the patient. As an alternative, stress radionuclide scintigraphy has been proposed, but this test is limited by variable sensitivity and specificity, high radiation exposure and a time-consuming protocol (35–39).

Electron beam computed tomography gives the chance to combine, in one session, calcium scanning and CT-angiography to evaluate the morphology of coronary arteries after injection of a contrast agent. However, no data on such a combined approach are available. Schmermund et al. (40) used EBCT-angiography alone in 28 patients and found a sensitivity of 82 ± 6% and a specificity of 88 ± 2% to detect significant stenoses. Achenbach et al. (41) studied 125 patients with EBCT angiography and reported a sensitivity of 92% and a specificity of 94% to diagnose high grade stenoses and occlusions; however, 124 (24.8%) of 500 coronary arteries had to be excluded from analysis because of poor image quality.

Calcium screening with EBCT should not be interpreted only in the context of severe coronary stenoses. Exclusion of stenosis does not guarantee a good prognosis, because small, unstable plaques may rupture and insignificant disease may progress to severe disease. Follow-up data, however, are not yet available for our patients. Our study only included symptomatic patients. "Symptoms" are a "soft" diagnostic criterion. Much of our data on prediction of stenosis severity by calcium screening might well be used to suggest the severity of stenoses in patients without symptoms (i.e., due to diabetes mellitus). However, calcium screening in asymptomatic individuals is mostly targeted at the early nonobstructive stages of atherosclerotic disease. A correlation could be found between the calcium score in asymptomatic patients and future cardiac events (42–44). The calcium score percentiles adjusted for age and gender are significantly higher in symptomatic versus asymptomatic patients with risk factors (45). Prospective studies with a sufficiently large number of patients are needed to determine the diagnostic accuracy, cost-effectiveness and potential benefit of identifying specific patients for primary prevention who may profit from secondary prevention goals and guidelines (46–48).

Clinical implications. In patients with typical angina (provoked by physical or emotional stress) and/or a definite diagnosis of myocardial ischemia on conventional stress tests, there is no indication for EBCT calcium screening because of the extremely high pretest likelihood of significant stenosis. Coronary angiography is required for the definite diagnosis and treatment in these patients. On the basis of our results, we see an indication for calcium screening in patients with atypical chest pain, especially if noninvasive tests are not feasible or inconclusive. Calcium screening with EBCT has the potential as a filter in symptomatic patients to reduce the number of invasive procedures which do not lead to intervention.

Acknowledgments

We gratefully acknowledge the expert consultant advice of Prof. Carl W. White, MD, Cardiovascular Division, University of Minnesota Medical School. We also thank Mrs. Anja Maass for technical assistance, Mrs. Regine Pulter for statistical workup, Mrs. Sibel Aydemir for statistical support and Mrs. Panjame Siebel for secretarial assistance.

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